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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,456	MULLIS, KARY B.	
	Examiner	Art Unit	
	David A. Saunders, PhD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-20 are pending and under examination.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, line 4 "the linker molecules" lacks antecedent basis.

In claim 16, line 4-7, references to "different epitopes on the immune response component" and to "same epitopes on the immune response component" are unclear, because the "immune response components" would not be understood by one of skill as having any "epitopes". It is taken that "the immune response component" can be an antibody or a T/B cell receptor (see para. [0041] of applicant's disclosure in US 2004/0185054). It is well known in the art that these antibodies or T-cell receptors would recognize B or T epitopes on the antigenic components serving as "the first binding sites". The "epitopes" are thus on "the first binding sites", rather than on "the immune response component".

In claim 16, lines 4-5 "the immune response component" lacks antecedent basis.

In claim 20, line 7 one cannot determine whether "or an immunological equivalent thereof" modifies "the first binding site" or the "humoral response" component of line 6.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

If one interprets claim 20 such that "or an immunological equivalent thereof" in line 7 modifies the "humoral immune response" component of line 6, then applicant has not described any "immunological equivalent" of the "humoral immune response" component. Other than B-cell receptors and B-cell secreted antibodies, the humoral immune system of an individual does not have any "immunological equivalent thereof ", in terms of binding capability and effector function.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

For purposes of stating prior art rejections, the instant claims have benefit of the instant filing date of 1/9/04. Instant claim 1 recites specifics not disclosed in parent application 10/696,770. Instant claim 20 recites a newly disclosed concept of increasing a humoral immune response against a target that normally elicits a cellular immune response.

Claims 1-2,4-5,7,13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Sallberg (US 5,869,232 or WO 95/29938).

For convenience, the examiner will only refer to the US reference by col. And line number. Sallberg discloses an "antigen/antibody specificity exchanger" (AASE) which corresponds to applicant's "immunity linker". Sallberg discloses the use of the AASE to "redirect a patient's antibodies"; such a process of "redirecting" is consistent with "increasing an immune response to a target" as recited in instant claim 1. See col. 3, line 67-col. 4, line 31; see also claims 12-17.

More specifically, the "antigen/antibody specificity exchanger" of Sallberg comprises:

A) an amino-acid sequence corresponding to an amino-acid sequence of an antibody which specifically binds to a certain antigen (e.g. "target" antigen).

B) a linker.

C) an amino-acid sequence to which a certain antibody (i.e. a pre-existing antibody) binds.

See Sallberg at col. 1, lines 58-65 and col. 2, lines 17-34, for example. Component A) of Sallberg corresponds to the instant "second binding site" and component C) of Sallberg corresponds to the instant "first binding site".

Dependent claim 2 is rejected, since there would be "pre-existing" immunity against antigens such as those disclosed at col. 4, lines 13-18. These antigens may be properly considered as "universal" because individuals in most societies would have been routinely and intentionally immunized (vaccinated) against such antigens.

Dependent claim 4 is rejected because Sallberg teaches that the pre-existing antibodies may be induced by a natural infection. See col. 4, lines 19-20.

Dependent claim 5 is rejected because Sallberg teaches that component A) can be constituted by a CDR or framework region (i.e. a "fragment") of an antibody.

Dependent claim 7 is rejected because the antigens corresponding to the instant "target" antigen are clearly "pathogens"; see, for example, the teaching of HIV as such a pathogen at col. 4, lines 13-31.

Dependent claim 13 is rejected because it is considered that the patients described by Sallberg at col. 4, lines 7-12 and 23-25 are patients who are "unable to mount an effective immune response to the target".

Dependent claim 15 is rejected because the teaching that method of using the the AASE is for “redirecting” a patient's antibodies is a teaching that use of the AASE is for “redirecting” the pateint’s humoral immune response.

Claims 1,2,13 and15 are rejected under 35 U.S.C. 102(b) as being anticipated by Krsmanovic et al (5,378,815).

Krsmanovic et al teach a method of immunizing against target cancer cells. They use a “conjugate” which corresponds to the instant “immunity linker” The “targeting agent” component of this conjugate corresponds to the instant “second binding site”. The “sensitizing agent” component of this conjugate corresponds to the instant “first binding site”. See col. 2, lines 18-col. 3, line 30; col. 4, line 26- col. 5, line 14, for example. Instant claim 1 is thus anticipated.

Regarding claim 2, note col. 4, lines 51-65.

Regarding claim 13, note col. 4, line 65-col. 5, line 5.

Regarding claim 15, the teaching that the "sensitizing" component (e.g. a toxoid antigen) of the "conjugate" binds to pre-existing antibodies thereto (e.g. see col. 4, lines 34-50) is consistent with the goal of increasing the patient's humoral immune response.

Claims 1-3,5 and13-14 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Marinkovich (US 2003/0108555).

Marinkovich teaches a method of immunizing/vaccinating against target cancer cells, so that cellular immunity against the cancer cells is enhanced. He uses a "conjugate" which corresponds to the instant "immunity linker". In the embodiments in which this conjugate contains a monoclonal antibody that recognizes cancer cells, this antibody corresponds to the instant "second binding site". The antigen component of this conjugate corresponds to the instant "first binding site". See para. [0014]-[0018] and [0039]-[0053], for example. Instant claims 1, 5 and 14 are thus anticipated.

Regarding claim 2, note para. [0016].

Regarding claim 3, note para. [0047] teaching that the Asp fl antigen can be either in purified form or recombinant form

Regarding claim 13, note para. [0001] teaching that cancer patients mount an ineffective immune response to cancers.

Claims 1-7 and 12-19 are rejected under 35 U.S.C. 102 (b) or (e) as being anticipated by Pouletty (WO 97/37690 or US 2006/0002891).

The WO and US references are equivalent in disclosure. The examiner will refer only to the US reference by col. And line no.

Pouletty teaches therapeutic methods that involve administering conjugates designated as "complexines" to a host. Such "complexines" correspond to the instant immunity linker. The complexines include a target binding moiety that corresponds to the instant "second binding site". The complexines also include a "selective member" that binds/interacts with a member of the immune system; this "selective member" corresponds to the instant "first binding site". The target binding moiety of Pouletty can

be a ligand for a cell surface receptor or an antibody or Fab fragment thereof directed to a cell surface receptor. The "selective member" of Pouletty can be an antigen to which to which the host has previously formed antibodies or T-cells. See, for example, para. [0018]-[0023]. From the above, instant claims 1 and 5-6 are anticipated.

Regarding claim 2, note teachings of host immunity against the "selective member" by virtue of immunizations in para [0023].

Regarding claim 3, note para. [0023] teaching that the "selective member" of the conjugate may be an anti-idiotypic antibody. In such case the antigen that has been used to sensitize the host and the anti-idiotypic antibody constitute "immunological equivalents" in that both would bind to pre-existing antibodies formed in the host.

Regarding claims 4 and 12, note teachings of host immunity against blood group antigens in para. [0023] and against alpha-gal epitopes in para [0024] and [0026].

Concerning claim 7, note para. [0030].

Concerning claim 13, note para. [0005]-[0006].

Regarding claims 14-15, note para. [0023] teaching that the selective member may bind to preexisting antibodies or to a T-cell. These selective members would thus serve, respectively, to enhance humoral or cellular immune responses in the host.

Regarding claims 16 and 18, note para. [0027]-[0028].

Regarding further dependent claim 17, note that, when the A+B+vaccine Ag is used as the therapeutic agent, the host would have preformed, natural antibodies against the A and/or B antigen.

Also, regarding claims 18-19, note Pouletty at Example 4. Therein the "complexine" conjugate has its target binding moiety constituted by a polyclonal anti-thymocyte globulin preparation (para. [0050]). Any polyclonal antibody preparation is inherently heterogeneous in its specificity (i.e. many epitopes on the thymocyte cell surface will be bound) and in its binding avidity. Thus both conditions a) and b) of instant claim 18 are met.

Claims 1-2,4-7 and 12-15 are rejected under 35 U.S.C. 102(b) or (e) as being anticipated by Low et al (US 2001/0031252 or US 7,033,594).

Low et al teach therapeutic methods in which a "ligand- immunogen conjugate" is administered to a host. The ligand-immunogen conjugate corresponds to the instant "immunity Linker". The ligand component of this conjugate corresponds to the instant "second binding site". The ligand of Low et al serves to target the conjugate to pathogenic cells, such as cancer cells or foreign pathogen cells. The immunogen of Low et al corresponds to the instant "first binding site". See '594 at col. 1, lines 13-21; col. 2, line 37-col. 3, line 19; col. 3, lines 41-63; col. 6, lines 13-32, for example. From the above instant claim 1 is anticipated.

Regarding instant claim 2, note '594 at col. 10, lines 15-23 teaching immunization/vaccination to induce a pre-existing host immune response.

For instant claims 4 and 12, note '594 at col. 10, lines 23-26 teaching that the pre-existing host immune response may be an innate response against the alpha-gal group.

Regarding instant claims 5-6, note '594 at col. 8, lines 5-10 teaching that the ligand component may be an antibody or Fab fragment thereof.

Regarding instant claim 7, note '594 at col. 6, line 54-col. 7, line 37 and col. 8, Lines 27-37 teaching that the target cells may be various pathogens and teaching specific ligands for the pathogens.

Regarding instant claim 13, note '594 at col. 1, Lines 25-44.

Regarding claims 14-15, note col. 9, lines 23-27 and col. 9, line 64-col. 10, line 2 teaching that the immunogen member of the conjugate may serve to redirect humoral or cellular immune responses in the host.

Claims 1,2,5-7 and13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Cowan (WO 01/32207).

Cowan teaches therapeutic treatments involving the use of a hapten -ligand conjugate, which corresponds to the instant "immunity linker". The hapten portion of this conjugate corresponds to the instant "first binding site"; the individual being treated has been previously immunized against the hapten. The ligand portion of the conjugate corresponds to the instant "second binding site"; this can be an antibody or fragment

thereof directed against a target antigen. See, for example, pages 6-7. From the above instant claims 1, 2, 5 and 18 are anticipated.

Regarding claim 6, note page 10.

For claim 7, note page 8, last para.

Regarding claim 13, note page 4, para. (5).

Regarding claims 14-15, note Example 4 (pgs 11-12) teaching that one can administer a hapten-ligand conjugate which has the hapten DNP, which is recognized by antibodies of the humoral immune system of the individual/subject. Alternatively, one can administer a hapten-ligand conjugate which has the hapten ABA-Tyr, which is recognized by cellular immune system of the individual/subject. Thus a subject administered one of these conjugates achieves either humoral or cellular immunity, respectively, to the target antigen.

Regarding claim 16, note Example 4 (pgs 11-12) teaching that one can administer two hapten-ligand conjugates. One conjugate has the hapten DNP, which is recognized by antibodies of the humoral immune system of the individual/subject. The other conjugate has the hapten ABA-Tyr, which is recognized by cellular immune system of the individual/subject. Thus a subject administered both of these conjugates achieves both humoral and cellular immunity to the target antigen. Since the humoral and cellular immune systems involve different "immune response components" the limitations of claim 16 are met, to the extent that the examiner can understand claim 16 (see 112, second rejection supra).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marinkovich, Pouletty, Low et al or Cowan, any or all in view of Rhodes (4,940,670).

Each of the primary references has been cited supra against claim 1. Each shows treatment of cancer with a conjugate that corresponds to the instant "immunity linker" for the case in which the instant "second binding site" is an antibody directed against an antigen on cancer cells.

Rhodes teaches the therapeutic treatment of cancer patients with immunoconjugates that have a therapeutic agent (e.g. a radionuclide) conjugated to an antibody directed to an antigen on cancer cells. Rhodes teaches that, because tumor cells are heterogeneous in their expression of various individual tumor antigens, it is advantageous to use a cocktail of immunoconjugates; each of the immunoconjugates forming such a cocktail has an antibody specific for a different antigen known to be present in the cancer patient's tumor.

It would thus have been obvious to have used a cocktail (i.e. a "population") of "immunity linkers" taught by any of the primary references, wherein the cocktail would contain various "immunity linkers" that differ from one another by virtue having different antibodies directed to different antigens that are present in a patient's tumor. By so doing one would have expected to be able to more effectively target tumors that have a heterogeneity in expression of tumor antigens.

Furthermore, among the primary references, the examiner finds motivation for use of such a cocktail, since Low et al teach (col. 9, lines 6-9) that one can use "combinations of ligand –immunogen conjugates to maximize targeting of the pathogenic cells for elimination". While Low et al give no further information about the composition of such combinations, it is considered that the teachings of Rhodes would have given one adequate direction in teaching one how to "maximize targeting of pathogenic cells" that are cancer/tumor cells.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13 and 15-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10-13 of copending Application No. 10/178,046. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims 1-13 and 15-19 and the copending claims are drawn to "increasing an immune response" (i.e. "immunizing") an individual against a target by using a "immunity linker molecule". The instant claims 1-13 and 16-19 are broad because, in the immunized individual, either the cellular or the humoral immune response may be increased. The copending claims are narrow, because the immunized individual is required to have a "pre-existing antibody" (i.e. a pre-existing humoral immune response) against the first site of the linker; thus, in the immunized individual, the humoral response would be increased. The instant broadly recited claims 1-13 and 15-19 encompass the more narrowly recited copending claims. Instant claim 15 and copending claim 8 are both drawn to a method of increasing a humoral response and thus encompass common subject matter. For these reasons a disclaimer is required.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of

copending Application No. 10/696,770. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending claims encompasses that of the instant claims.

Specifically, the copending claims are silent as to the type of immune response induced against the target. The instant claims more specifically recite that the immune response induced against the target is a cellular or a humoral immune response (e.g. instant claim 1, conclusion thereof, and claims 14-15). It is taken that the increased immune response of the copending claims can encompass a cellular or a humoral immune response. Note, for example, the teachings that, when the universal immunogen (which corresponds to, or contains, the first binding site of the immunity linker) is administered to an individual, "such administration causes the individual to mount the expected, normal immune response, generally either a cellular or a humoral immune response." See US 2004/0146515 at para. [0013]. Since the copending claims clearly encompass what is recited in the instant claims, a disclaimer is required.

- This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Larocca et al (6,054,312) teach phage particles which display a ligand (e.g. an antibody binding site) directed to a target cell (e.g. a tumor cell). The phage genome encodes a therapeutic agent that is delivered to the target cell. In one embodiment, the encoded therapeutic agent is alpha-1,3-galactosyl transferase; expression thereof on tumor cells allows complement mediated cell killing. See column 31, lines 50-52. Since these phages do not have a "first binding site" against which an "individual has a preexisting immune response" (these phages, rather, encode a "first binding site"), as required by instant claim 1, instant dependent claims 8-11 are not impacted by this reference. If applicant deems that the instant disclosure would provide for a broader interpretation of the recitation of "first binding site" in instant claim 1, applicant is required to amend around this reference.

Sallberg et al (6,933,366, cited on Form 1449) teach antigen/antibody specificity exchangers in the manner of Sallberg ('232) cited supra. Sallberg et al ('366) teach expression systems that include microorganisms, such as bacteria transformed with recombinant bacteriophage DNA. See col. 17, lines 11-14. These are expression systems taught in the context of the manufacture of antigen/antibody specificity exchangers; the expressed and purified product would be administered to a subject/individual. There is no teaching that the bacteria transformed with recombinant bacteriophage DNA would be administered to a subject/individual. Instant claims 8-11 are not impacted by this reference.

Instant claims 8-11 and 20 contain limitations allowable over the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 9/7/06 DAS

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
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